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10/803,180	03/18/2004	Michele Cargill	CL1511ORD	6182

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/803,180	CARGILL ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,39-45,56 and 59-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,39-45,56 and 59-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 36, 39-45, 56 and 59-84 are pending and examined on the merits.

1. Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application on 04/06/2009 after final rejection on. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 02/05/2009 has been entered.

This Office Action is in reply to Applicants' correspondence of 02/05/2009.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put this application in condition for allowance. New grounds of rejection and objection are presented in this Office Action. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is **NON-FINAL**.

New Claim Objections

2. Claim 39 is objected to because of the following informalities:

Claims 39 recited the gene symbol TRIP, where at the first instance of the gene symbol in the claims the symbol should be accompanied by the full gene name, for example: "the genomic sequence of the TRIP (TRAF interacting protein) gene".

Appropriate correction is required.

Withdrawn Claim Rejections - 35 USC § 112 1st ¶ - New Matter

3. The rejection of claim 74 under 35 U.S.C. 112, first paragraph, for recitation of new matter, as set forth on pages 2-3 of the Office Action of 11/05/2008, is **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 1st ¶ - New Matter

4. Claims 79-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The rejected claims require correlating detected genotypes with predisposition for coronary stenosis. However the methods of the applications as originally filed are drawn to diagnosis of autoimmune diseases, and particularly rheumatoid arthritis. Applicants' have not pointed to any portion of the specification as originally filed which provides basis for methods related to coronary stenosis. As such, the limitations of the rejected claims are new matter.

Withdrawn Claim Rejections - 35 USC § 112 1st ¶ - Written Description due to Improper Incorporation by Reference

5. The rejection of claim 74 under 35 U.S.C. 112, first paragraph, as set forth on pages 3-4 of the Office Action of 11/05/2008, is **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 1st ¶ - Written Description

6. Claims 74 and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 74 ad 75 require 'testing nucleic acid from said human subject for the presence or absence of single nucleotide polymorphism (SNP) hCV163035' and further require, for example as recited in claim 74, 'wherein A at the SNP based on the sequence orientation of SEQ ID NO: 5502'. In the case of the rejected claims the particular location of a detected SNP is critical for the practice of the claimed method. However, in the instant case the claims do not indicate with particularity the sequence context of the required nucleotide content. It is noted that while the specification as originally filed does recite the term 'hCV163035', there is not in fact a limiting definition presented in the specification as to what is required for the recited SNP. Furthermore, the term 'hCV163035' appear to be an internal identification number specific to Applicants' nomenclature for identifying nucleotide variations, and is not an art recognized term to specify some particular nucleotide content.

In the instant case, the rejection may be overcome if the phrase 'testing nucleic acid from said human subject for the presence or absence of single nucleotide polymorphism (SNP) hCV163035' is amended to recite, for example as relevant to claim 74, 'detecting the genotype comprising an A at single nucleotide polymorphism (SNP) hCV163035, wherein detecting an A at position 101 of SEQ ID NO: 5502 indicates the presence of a genotype comprising an A at single nucleotide polymorphism (SNP) hCV163035'.

Maintained Claim Rejections - 35 USC § 112 1st¶ - Scope of Enablement modified as necessitated by amendments to the claims

7. Claims 36, 39-45, 56 and 59-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification:

While being enabling for,

> A method for identifying a human individual who has a decreased risk for developing positive autoantibody rheumatoid factor (RF+) rheumatoid arthritis (RA) comprising:
> obtaining a biological sample from said individual wherein the biological sample comprises nucleic acids; and
> detecting the nucleotide content at position 101 of SEQ ID NO: 5502 or the complement of SEQ ID NO: 5502 in said nucleic acids;
> wherein, detecting the nucleotide A at position 101 of SEQ ID NO: 5502, or detecting the nucleotide T at position 101 of the complement of SEQ ID NO: 5502, identifies the individual as having a decreased risk for developing RF+ RA.

Or

> A method for identifying a human individual who has an increased risk for developing positive autoantibody rheumatoid factor (RF+) rheumatoid arthritis (RA) comprising:
> obtaining a biological sample from said individual wherein the biological sample comprises nucleic acids; and
> detecting the nucleotide content in both alleles at position 101 of SEQ ID NO: 5502 or the complement of SEQ ID NO: 5502 in said nucleic acids;
> wherein, detecting the nucleotide G at position 101 of both alleles of SEQ ID NO: 5502, or detecting the nucleotide C at position 101 of the complement of both alleles of SEQ ID NO: 5502, identifies the individual as having an increased risk for developing RF+ RA.

does not reasonably provide enablement for diagnostic methods which do not require the detection of particular nucleotide content, or methods wherein a correlation is made between nucleotide content and risk for developing coronary stenosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Nature of the invention and breadth of the claims

The claims of the instant application are drawn to methods for identifying an individual who has an increased or decreased risk for developing RA.

The recitation of the steps of the claimed methods do not in fact require the detection of any particular nucleotide content. The claims are drawn to methods steps wherein a nucleic acid is tested for the presence or absence of a SNP, but there is no method step which requires that any particular content is detected or identified in a subject's nucleic acids. Furthermore, with particular regard to claims 74 and 75, the recitation of the term 'hCV163035' does not provide any particular required position of the, for example as recited in claim 74, 'A at the SNP based on the sequence orientation of SEQ ID NO: 5502'.

The claims encompass the identification of increased coronary stenosis risk correlated with the G/G or C/C genotype, and the identification of decreased coronary stenosis risk correlated with the absence of a G/G or C/C genotype.

The nature of the invention requires knowledge of an association between a broad variety of nucleic acid content and content that is not required to be detected and altered risk of having RA and coronary stenosis.

Direction provided by the specification and working example

The instant specification teaches that an association study of a SNP and a specific disorder involves determining the presence or frequency of the SNP allele in biological samples from individuals with the disorder (i.e. cases) of interest and comparing the information to that of control individuals who do not have the disorder (p.7 ln.28 – p.8 ln.4).

The instant specification provides an example of an association study of the polymorphic content at position 101 of SEQ ID NO: 5502, which may be either an A or a G, and is associated with the internal identification 'hCV163035' and the SNP database entry 'rs2276864'. The specification teaches that the frequency of the particular allele was analyzed in two (p.120 ln.26 – p.121 ln.11) patient populations: a Discovery Set (475 unrelated cases and 475 controls who were RF+); and a Replication Set (840 cases from 463 families and 926 controls). The specification further indicates that the Replication set was analyzed in totality (i.e. an 'all' stratum) after stratification of the subjects into an RF+ stratum (p.12; p.121 ln.28).

The specification teaches the specific association of the A allele (i.e. an A nucleotide a position 101 of SEQ ID NO: 5502) with a decreased risk of RA as the A allele is found at a significantly higher frequency in control samples in the Discovery Set and the Replication Set (Table 6). It is noted that Table 6 designates the 'T' allele as

associated with the decreased risk of RA, and the specification indicates that nucleotide content may be described as the reverse of the nucleotide content at the position (e.g. p.20, lns.25-30), thus the T allele of the reverse complement of SEQ ID NO: 5502 is the A allele of SEQ ID NO: 5502. The analysis of the Discovery Set is an analysis of RF+ RA, because as stated in the specification all cases of the Discovery Set were RF+ (p.120 ln.29). While the instant specification provides that the A allele is indicative of a decreased risk for RA in the Replication Set in the 'All' Stratum, the specification provides no indication as to how many of the cases in the Replication Set were either RF+ or RF- (i.e. while the specification indicates that the Replication Set had 840 patients, it is not known if there were enough of both RF+ and RF- individuals to make data regarding the 'All' stratum significant for both RF+ and RF-). Thus it is not possible to determine from the data of Table 6 indicating a significant relationship between the A allele of SEQ ID NO: 5502 and decreased risk of RA is in fact significant within the RF- population of cases under analysis. Thus while the data of specification teaches an association of the A allele with decreased risk of RF+ RA, it is not clear from the specification if the A allele is specifically associated in the same way, or in a significant fashion, with RF- RA.

Because the claims do not clearly specify the detection of homozygous G content at position 101 of SEQ ID NO: 5502 in the determination of increased risk of RF+ RA (it is noted that independent claims 36 and 56 do not require analysis of both alleles of SEQ ID NO: 5502), where determination of heterozygosity at the position (i.e. an individual with one of each allele) would be detection of both alleles, it is relevant to

point out that the data presented in the instant specification (i.e. Table 6) indicates only that the presence of a T allele (which is an A allele in SEQ ID NO: 5502) is indicative of a decreased risk of RF+ RA. The data does not stratify the data based on genotype (i.e. CC vs CT vs TT), and thus appears to present only that detection of a T allele (i.e. either in a CT or TT genotype) is indicative of decreased risk of RF+ RA as compared to a CC individual, and does not provide a comparison of the relative risk of RF+ RA in a CT versus a CC individual. Thus while it is possible for the data to support that the presence of an A at position 101 of SEQ ID NO: 5502 is indicative of decreased risk of RF+ RA (because presence of either an AA or AG genotype would have a decreased risk), the data would not support making a determination based only on the presence of a single G allele (because it would not be known if the individual has a GG (increased risk) genotype or an AG (decreased risk) genotype).

The instant specification provides only the association analysis of either an A or a G at position 101 of SEQ ID NO: 5502 (as consonant with the Election), and does not provide any analysis of any other polymorphic content at any other position of SEQ ID NO: 5502. With regard to claim 74, it is noted that the requirement for the recited 'rs2276864' has been rejected previously in this Office Action for issues under 35 112 1st. However it is noted that claim 74 recites 'the presence of T or its complement at the SNP', where rs2276864 is a specific SNP (i.e. particular polymorphic content in a particular context) that is either a T or a C, where the complement of T (as encompassed by the claims) is an A.

The instant specification does not appear to provide for any particular association between a genotype and risk of coronary stenosis, as required by claims 79-84.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to the detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach an association between any polymorphism at position 101 in SEQ ID NO: 5502 and altered risk for developing RA or coronary stenosis. And because the language of the claims encompass methods wherein the method steps comprise testing for the presence or absence of a SNP, and the methods steps do not in fact required the detection of any specific content, it is relevant to point out the unpredictability in associating any particular SNP with a particular phenotypic trait. This point is further relevant to claims 79-83 which require an association between genotype and risk of coronary stenosis, where the specification does not appear to demonstrate any such association. For example, Hacker et al teaches that they were unable to confirm an association between a gene mutation and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627).

Quantity of experimentation required

A large amount of experimentation would have to be performed in order to make and use the claimed invention in the full scope of the claims. Given that the claims do not recite any step wherein any particular nucleotide content is detected, such experimentation would include examining an association of any nucleotide content with the risk of RF+ RA. Furthermore, experimentation would be required to establish that particular genotypes, as required for claims 79-84, are indicative of coronary stenosis risk. This would involve large case:control studies in multiple human populations. Even if such an analysis were to be performed, there is no assurance that one would find any significant associations beyond those specifically taught in the particular example of the instant specification.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the few specific working examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention in the full scope of the claims.

Response to Remarks

Applicants have argued (p. 8 of Remarks of 02/05/2009) that the instant claims have been amended so as to be commensurate with the scope indicated as enabled by the Examiner. The argument has been considered but is not persuasive to withdraw the rejection. As particularly set forth in the indication of the method enabled by the instant

specification, the claims are enabled for methods in which particular nucleotide content is detected and indicative of RF+ RA risk. In the case of the instant claims, merely recite methods of 'testing for the presence or absence' of a SNP, and thus do not have a step wherein any particular content is required to be detected. Additionally, there does not appear to be any teaching in the specification of a reliable association between genotypes and risk of coronary stenosis, as recited in the claims.

The rejection as set forth is **MAINTAINED**.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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/Stephen Kapushoc/